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REMARKS

After entry of this paper, claims 4-10, 12, 13, and 15-29 are pending. Applicants reserve the right to prosecute the original and any deleted subject matter in a continuation application filed during the pendency of the present application.

35 USC § 103(a) Rejection

Claims 4-10, 12, 13, 15, and 21-29 are rejected under 35 USC § 103(a) over Liu et al, 1999 Arterio. Thromb. Vasc. Biol., 19:2207-2213 ("Liu") in view of Drayna et al, 1987 Nature, 327:632-634 ("Drayna"), Taylor et al., 1999 Drug Disc. Today, 4(12):562 ("Taylor"), US Patent No. 5,801,154 ("Baracchini"), and US Patent No. 5,955,443 ("Bennett").

The Examiner has alleged that it would have been obvious to make modified antisense oligos targeted to Applicants' instant SEQ ID NO: 3 protein because both Liu and Drayna teach DNA for human cholesteryl ester transfer SEQ ID NO:3, because Taylor teaches that one may inhibit expression of any protein using known cDNA sequences by generating antisense oligos (alleging that only 3-6 oligos need be screened to find one that inhibits its target 66-96%); and because Baracchini and Bennett teach that antisense oligos may be targeted to the 3' UTR of the target (which is region 1631-1769 of SEQ ID NO: 3), and teach various modifications of antisense compounds.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

Liu refers to the nonviral gene delivery system formed by the complex formed between an LDL-receptor binding peptide, i.e., an ApoE peptide, and a single 21-mer phosphorothioated antisense oligonucleotide directed against nb 329-349 of human CETP. While the CETP

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expression decreased after transfection with the complex, the activity started to recover after 48 hours,

"in contrast *no difference* was found after transfection with S-ODN/dpGapoE or *naked* AS-ODNs compared with controls (Figure 2)." (emphasis added; Liu, page 2209, col. 2, 3rd full para).

The single antisense compound used alone in Liu produced *no decrease* in CETP expression when compared to a control. Thus, Liu's only teaching relating to antisense oligos to CETP appears to be that complexation with a binding peptide of some kind is *required* for inhibition of the CETP expression.

Drayna teaches the cloning and sequencing of a human CETP DNA. Drayna teaches nothing about CETP other than *suggestions* for possible biological activities. Drayna also does not teach or suggest antisense compounds or any sequences within CETP for successful hybridization of any antisense compounds.

Thus, Drayna adds nothing more to Liu to suggest the claimed invention of the present application. The remaining three references, which do not even mention CETP, fail to add the necessary disclosure to the mere disclosure of the sequence of CETP by Liu and Drayna and the implication in the data of Liu that complexation with a binding peptide of some kind is *required* for inhibition of the CETP expression.

Baracchini and Bennett are prior US patents of the same assignee, and refer to antisense compounds to multidrug resistance-associated protein and namely platelet endothelial cell adhesion molecule-1 (PECAM-1), respectively. Both targets are completely unrelated protein

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to CETP. Neither Baracchini nor Bennett teaches or suggests antisense oligonucleotides 8-50 nucleobases in length targeted to CETP nucleic acid molecules, or any region of a CETP nucleic acid molecule, that inhibit express of CETP. While Baracchini and Bennett teach methods of modifying the antisense oligonucleotides to their own targets, and do suggest various regions of their own targets for direction of possible antisense oligonucleotide targeting, the inclusion of the teachings of these two documents do not provide a reasonable expectation of success in obtaining oligonucleotide compounds that would inhibit CETP by targeting a portion of the 3'UTR of CETP, as recited in Applicants' claim 1.

Nothing in Liu, Drayna, Baracchini or Bennett directs a person of skill in the art to a *specific portion* of the 3' UTR of CETP as desirable target for the development of antisense oligonucleotides that can inhibit CETP. Note that the entire 3'UTR of CETP spans nb 1613-1787 of SEQ ID NO: 3. Applicants' claim 1 covers only nb 1631 to 1769 of that sequence. Further nothing in Drayna, Baracchini or Bennett explains the "teaching away" of Liu's use of a naked antisense oligonucleotide directed to a different portion of the CETP sequence than is recited in claim 1.

Thus, Liu, Drayna, Baracchini and Bennett do not provide sufficient teaching to suggest Applicants' claimed invention.

The addition of the Taylor review article to the above four reference adds nothing to the above reference combination that would make obvious the invention of the pending amended claims.

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In fact, Taylor makes a misleading and unsupported allegation about the ease and straightforward manner of determining target sites on a gene that permit one to identify suitable antisense oligonucleotides of a high degree of inhibition for any gene. The Examiner has asserted that Taylor teaches that

"with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%."

Applicants assert that this blanket statement in Taylor conveys a misleading impression to the examiner that identification of target sites that can be bound by antisense oligonucleotides to significantly inhibit gene expression is simple and expected. (Note that Liu's single oligo appears to contradict the readiness of obtaining an antisense oligo that inhibits without additional modification in the form of complexation to a delivery peptide.) In fact, such techniques do not produce such "expected" and simple results as stated by Taylor.

Taylor fails to teach the name of the software screening program that can deliver such stated results. Taylor also fails to identify the manufacturer of such software screening program. As support, Applicants have enclosed a Declaration executed by Dr. Susan Freier, one of the co-inventors of this application and one of skill in the art of oligonucleotide technology. Dr. Freier has attested that she is not aware of any software screening program that can provide the results stated in Taylor. In addition, Dr. Freier declares in paragraph 12 of the

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declaration that Taylor does not enable her to practice that which is discussed in Taylor.

In view of the attached Declaration, Applicants request that Taylor be withdrawn as a basis for combination with the other references in making this rejection. As the obviousness rejection is based upon a combination of Liu, Drayna, Baracchini, Bennett and Taylor, the removal of Taylor as a reliable reference defeats this ground of rejection.

Thus, the combination of the cited documents does not provide any suggestion of the antisense sequences of claim 1. An obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make antisense compounds to target CETP. As the Examiner is aware, "obvious to try" is not a proper basis for an obviousness rejection. The combination of Liu, Drayna, Bennett, and Baracchini, with or without the addition of Taylor, does not provide any motivation nor expectation of success that if one did target the *specifically claimed* sequences of the present claims, that one would obtain a desired inhibitory result. This combination of art does not make obvious the presently claimed invention.

The only source of the required motivation to make and use antisense compounds directed to specific sequences of CETP recited in claim 1, which sequences are not identified by either cited reference, is provided by the Applicants' own specification. The only teachings which supply the necessary motivation and expectation of success that such a composition would be useful are provided by the instant

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specification. Obtaining the motivation for combination of the prior art cannot properly be provided by Applicants' own disclosure. Applicants maintain that the combination of the cited prior art, when the teachings are taken as a whole, fails to supply both the motivation and a reasonable expectation of success required to set forth obviousness of the pending claims.

The examiner has selected only isolated components from the references, ignoring other teachings of those same references. For example, only the generic teachings of Baracchini or Bennett with respect to antisense compounds are selected, without regard to the fact that Baracchini or Bennett was directed to a completely different (both structurally and functionally) protein, MDR or PBCAM-1. The rejection combines these selected components with Drayna's admitted *speculations* to use CETP to purportedly make a *prima facie* case of obviousness of the claimed invention, which ignoring the contradictory evidence of antisense inhibition provided in Liu. It is wholly inconsistent with established patent law that only that portion of each cited document which supports the examiner's position is relied upon in the rejection, while the remaining teachings of the combined cited documents are ignored as if irrelevant. This type of construction of an obviousness rejection disregards the standard patent law that references must be taken as a whole, not in pieces.¹

¹ *In re Oetiker*, 977 F.2d 1443, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992)

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The examiner would find no reason to have combined the teachings of Baracchini or Bennett with Drayna or Liu initially without the impermissible application of hindsight. The only motivation to perform such a combination of components is derived from Applicants' disclosure. The combination of these two prior art references to reject the pending claims of the present application is based simply on a prior reading of Applicants' invention. The examiner may not use Applicants' disclosure as a blueprint for piecing together prior art to defeat patentability in an improper manner.

One of skill in the art would not have made this combination of elements, i.e., a description of the cloning of CETP combined with a disclosure relating to anti-sense compounds that hybridize to MDR or PECAM-1, without the impermissible application of hindsight.² The examiner's reliance on hindsight is clearly improper. The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious, unless the prior art suggested the desirability of the modification. As discussed above, the prior art references in combination and taken as a whole do not suggest the claimed invention.

What the Office Action appears to suggest is that the claimed invention would have been obvious because it would have been possible to modify Applicants' oligonucleotide compounds to CETP in a similar manner as described for MDR

² See, e.g., *In re Dembiczak*, 50 USPQ2d 1614, 1616-1617 (Fed. Cir. 1999)

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or PECAM-1. The mere possibility that the prior art can be modified, however, does not itself provide the requisite motivation to do so.³ The mere possibility for modification and improvement is not the "motivating force" that the Patent Office Board of Appeals and the Federal Circuit have invariably required. If it were, then no modification would ever lack motivation since some change is always possible. Quite to the contrary, an invention is obvious under the patent laws only when the claimed means for effecting an improvement -- as opposed to the possibility of trying any and all means -- is suggested by the prior art⁴. Significantly, none of the cited references would have motivated persons of ordinary skill to make the substantial modifications that would have been necessary to produce the claimed invention. It is only with the improper use of hindsight and with the benefit of the Applicants' disclosure that one can discern the desirability of the particular invention now claimed.

Therefore, even if one skilled in the art were motivated to combine the cited references in the manner indicated in the Office Action (and Applicants maintain that no such motivation has been established), one skilled in the art would not have had a reasonable expectation of success.

³ *In re Dien*, 152 USPQ 550 (CCPA 1967) (incentive to seek improvement of existing process held to not render change made by applicant obvious, even where the change was one capable of being made from theoretical point of view).

⁴ *In re Shaffer*, 108 USPQ 326 (CCPA 1956) (references, viewed by themselves and not in retrospect, must suggest doing what applicant has done).

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For the reasons set forth above, Applicants submit that this rejection may be properly withdrawn as against the pending claims.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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